

1 PRESCRIBING INFORMATION

2 **ADVAIR DISKUS[®] 100/50**

3 (fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

4

5 **ADVAIR DISKUS[®] 250/50**

6 (fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)

7

8 **ADVAIR DISKUS[®] 500/50**

9 (fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)

10

11 *As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg

12

13 **For Oral Inhalation Only**

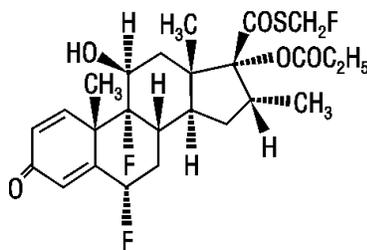
14

15 **WARNING:** Data from a large placebo-controlled US study that compared the safety of
16 salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed
17 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13
18 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see
19 WARNINGS).

20 **DESCRIPTION**

21 ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are
22 combinations of fluticasone propionate and salmeterol xinafoate.

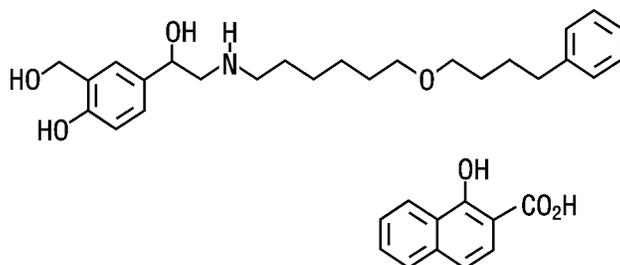
23 One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having
24 the chemical name *S*-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-
25 oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:



29 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and
30 the empirical formula is C₂₅H₃₁F₃O₅S. It is practically insoluble in water, freely soluble in
31 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

32 The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta₂-adrenergic
33 bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt
34 of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- α -1-[[[6-(4-phenylbutoxy)

35 hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has
36 the following chemical structure:
37



38
39
40 Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the
41 empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in
42 ethanol, chloroform, and isopropanol; and sparingly soluble in water.

43 ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are
44 specially designed plastic devices containing a double-foil blister strip of a powder formulation
45 of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister
46 on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone
47 propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of
48 salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins).
49 Each blister contains 1 complete dose of both medications. After a blister containing medication
50 is opened by activating the device, the medication is dispersed into the airstream created by the
51 patient inhaling through the mouthpiece.

52 Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg
53 of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS
54 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.
55 In adult patients with obstructive lung disease and severely compromised lung function (mean
56 forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean peak inspiratory
57 flow (PIF) through a DISKUS[®] inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

58 Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to
59 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF
60 of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with
61 asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range,
62 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to
63 125.6 L/min) for the 8-year-old patient set (N = 20).

64 The actual amount of drug delivered to the lung will depend on patient factors, such as
65 inspiratory flow profile.

66 CLINICAL PHARMACOLOGY

67 **Mechanism of Action: ADVAIR DISKUS:** Since ADVAIR DISKUS contains both
68 fluticasone propionate and salmeterol, the mechanisms of action described below for the

69 individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of
70 medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor
71 agonist) that have different effects on clinical and physiological indices.

72 **Fluticasone Propionate:** Fluticasone propionate is a synthetic trifluorinated corticosteroid
73 with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations
74 have established fluticasone propionate as a human glucocorticoid receptor agonist with an
75 affinity 18 times greater than dexamethasone, almost twice that of
76 beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone
77 dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor
78 assay in man are consistent with these results.

79 Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have
80 been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes,
81 macrophages, and neutrophils) and mediator production or secretion (e.g., histamine,
82 eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These
83 anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

84 Inflammation is also a component in the pathogenesis of chronic obstructive pulmonary
85 disease (COPD). In contrast to asthma, however, the predominant inflammatory cells in COPD
86 include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in
87 the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone
88 propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of
89 COPD.

90 **Salmeterol Xinafoate:** Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies
91 and in vivo pharmacologic studies demonstrate that salmeterol is selective for
92 beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist
93 activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times
94 more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
95 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
96 predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart
97 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors
98 has not been established, but they raise the possibility that even highly selective beta₂-agonists
99 may have cardiac effects.

100 The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at
101 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes
102 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic
103 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition
104 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

105 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast
106 cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung.
107 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits
108 platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when

109 administered by the inhaled route. In humans, single doses of salmeterol administered via
110 inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

111 **Pharmacokinetics: ADVAIR DISKUS: Adult and Adolescent Patients 12 Years of**
112 **Age and Older:** Following administration of ADVAIR DISKUS to healthy adult subjects, peak
113 plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of
114 salmeterol were achieved in about 5 minutes.

115 In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was
116 administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were
117 administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol
118 powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean
119 peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL,
120 respectively, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no
121 significant changes in systemic exposures of fluticasone propionate and salmeterol.

122 In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was
123 administered to 45 adolescent and adult patients with asthma. One (1) inhalation twice daily of
124 the following treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate
125 powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate
126 powder 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate
127 averaged 57, 73, and 70 pg/mL, respectively, indicating no significant changes in systemic
128 exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in
129 this repeat-dose study.

130 No significant changes in excretion of fluticasone propionate or salmeterol were observed.
131 The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR
132 DISKUS was administered, which is similar to that reported when fluticasone propionate was
133 given concurrently with salmeterol or when fluticasone propionate was given alone (average,
134 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of
135 ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

136 **Pediatric Patients:** In a clinical study conducted in patients with asthma aged 4 to
137 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes
138 after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using
139 the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the
140 plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the
141 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

142 **Special Populations:** Formal pharmacokinetic studies using ADVAIR DISKUS have
143 not been conducted to examine gender differences or in special populations, such as elderly
144 patients or patients with hepatic or renal impairment.

145 **Drug Interactions:** In the repeat- and single-dose studies, there was no evidence of
146 significant drug interaction in systemic exposure between fluticasone propionate and salmeterol
147 when given as ADVAIR DISKUS.

148 **Fluticasone Propionate: Absorption:** Fluticasone propionate acts locally in the lung;
149 therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled
150 and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone
151 propionate is negligible (<1%), primarily due to incomplete absorption and presystemic
152 metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered
153 to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from
154 the DISKUS device in healthy volunteers averages 18%.

155 Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma
156 (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone
157 propionate inhalation powder using the DISKUS device. The mean fluticasone propionate
158 plasma concentration was 110 pg/mL.

159 Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD
160 averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily
161 (N = 30) via the DISKUS device.

162 **Distribution:** Following intravenous administration, the initial disposition phase for
163 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.
164 The volume of distribution averaged 4.2 L/kg.

165 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.
166 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly
167 bound to human transcortin.

168 **Metabolism:** The total clearance of fluticasone propionate is high (average,
169 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only
170 circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone
171 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had
172 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of
173 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other
174 metabolites detected in vitro using cultured human hepatoma cells have not been detected in
175 man.

176 **Elimination:** Following intravenous dosing, fluticasone propionate showed
177 polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours.
178 Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the
179 remainder excreted in the feces as parent drug and metabolites.

180 **Special Populations: Hepatic Impairment:** Since fluticasone propionate is
181 predominantly cleared by hepatic metabolism, impairment of liver function may lead to
182 accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease
183 should be closely monitored.

184 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 16 male
185 patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using
186 the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg
187 twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

188 **Age:** No relationship between fluticasone propionate systemic exposure and age was
189 observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

190 **Other:** Formal pharmacokinetic studies using fluticasone propionate have not been
191 conducted in other special populations.

192 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.
193 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor
194 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18
195 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was
196 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate
197 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable
198 (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{\max}
199 averaged 11.9 pg/mL [range, 10.8 to 14.1 pg/mL] and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL [range,
200 4.2 to 18.8 pg•hr/mL]). Fluticasone propionate C_{\max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range,
201 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,
202 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This
203 significant increase in plasma fluticasone propionate exposure resulted in a significant decrease
204 (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

205 Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are
206 coadministered with fluticasone propionate. In a drug interaction study, coadministration of
207 orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted
208 in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had
209 no effect on urinary excretion of cortisol.

210 In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone
211 propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect
212 fluticasone propionate pharmacokinetics.

213 **Salmeterol Xinafoate:** Salmeterol xinafoate, an ionic salt, dissociates in solution so that the
214 salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed,
215 metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma
216 levels do not predict therapeutic effect.

217 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low
218 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
219 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
220 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7
221 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
222 167 pg/mL at 20 minutes and no accumulation with repeated doses.

223 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages
224 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much
225 higher concentrations than those achieved following therapeutic doses of salmeterol.

226 **Metabolism:** Salmeterol base is extensively metabolized by hydroxylation, with
227 subsequent elimination predominantly in the feces. No significant amount of unchanged
228 salmeterol base was detected in either urine or feces.

229 **Elimination:** In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as
230 salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was
231 eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination
232 half-life was about 5.5 hours (1 volunteer only).

233 The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly
234 protein bound (>99%) and has a long elimination half-life of 11 days.

235 **Special Populations: Hepatic Impairment:** Since salmeterol is predominantly
236 cleared by hepatic metabolism, impairment of liver function may lead to accumulation of
237 salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

238 **Other:** Formal pharmacokinetic studies using salmeterol base have not been conducted
239 in other special populations.

240 **Pharmacodynamics: ADVAIR DISKUS: Adult and Adolescent Patients:** Since
241 systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose,
242 higher doses were used to produce measurable effects. Four (4) studies were conducted in
243 healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR
244 DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given
245 concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study
246 using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a
247 repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50,
248 fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose
249 study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg
250 alone, or placebo. In these studies no significant differences were observed in the
251 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and
252 glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone
253 propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic
254 effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR
255 DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the
256 hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant
257 differences across treatments were observed in 24-hour urinary cortisol excretion and, where
258 measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone
259 propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy
260 subjects.

261 **Asthma:** In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12
262 years of age and older with asthma, no significant differences were observed in the systemic
263 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and
264 glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and
265 adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS

266 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose
267 and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

268 In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50
269 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone
270 propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg
271 alone. No significant differences across treatments were observed in plasma cortisol AUC after
272 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

273 In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50
274 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder
275 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in
276 response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with
277 ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal
278 response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who
279 received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients
280 who received salmeterol.

281 **Chronic Obstructive Pulmonary Disease:** In clinical studies with ADVAIR
282 DISKUS in patients with COPD associated with chronic bronchitis, no significant differences
283 were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the
284 individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS
285 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the
286 fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the
287 placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5)
288 of these 8 subjects had a prolonged QTc interval at baseline.

289 In a 24-week study, 130 patients with COPD associated with chronic bronchitis received
290 continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of
291 twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder
292 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or
293 supraventricular arrhythmias and heart rate were observed among the groups treated with
294 ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the
295 fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the
296 group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of
297 nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone
298 propionate 500 mcg treatment groups).

299 Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in
300 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate
301 powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to
302 increase cortisol production in response to stress, as assessed by short cosyntropin stimulation,
303 remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR
304 DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL
305 assessed by high-performance liquid chromatography) after dosing, compared with 2 patients

306 (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol
307 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early
308 discontinuation from study.

309 **Pediatric Patients:** In a 12-week study in patients with asthma aged 4 to 11 years who
310 were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was
311 compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via
312 the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks
313 of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol
314 excretion was also similar between the 2 groups.

315 **Fluticasone Propionate: Asthma:** In clinical trials with fluticasone propionate inhalation
316 powder using doses up to and including 250 mcg twice daily, occasional abnormal short
317 cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted
318 both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence
319 of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out
320 with the DISKHALER[®] inhalation device in 64 patients with mild, persistent asthma (mean
321 FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo,
322 no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin
323 infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1
324 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing
325 at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had
326 an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or
327 2 years.

328 **Chronic Obstructive Pulmonary Disease:** In a 24-week study, the steady-state
329 fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of
330 patients with COPD associated with chronic bronchitis (N = 86) randomized to twice-daily
331 fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate
332 inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured
333 across a 12-hour dosing interval following at least 4 weeks of dosing. Serum cortisol
334 concentrations following 250 and 500 mcg twice-daily dosing were 10% and 21% lower than
335 placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

336 **Salmeterol Xinafoate:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can
337 produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium
338 (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure)
339 associated with salmeterol occur with similar frequency, and are of similar type and severity, as
340 those noted following albuterol administration.

341 **Asthma:** The effects of rising doses of salmeterol and standard inhaled doses of albuterol
342 were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg
343 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the
344 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and
345 adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent

346 continuous electrocardiographic monitoring during two 12-hour periods after the first dose and
347 after 1 month of therapy, and no clinically significant dysrhythmias were noted.

348 **Chronic Obstructive Pulmonary Disease:** In 24-week clinical studies in patients
349 with COPD associated with chronic bronchitis, the incidence of clinically significant
350 electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically
351 significant conduction abnormalities, clinically significant arrhythmias) was lower for patients
352 who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or
353 ADVAIR DISKUS) compared with placebo (3%, 10 of 370 subjects).

354 No significant differences with salmeterol 50 mcg alone or in combination with fluticasone
355 propionate as ADVAIR DISKUS 500/50 was observed on pulse rate and systolic and diastolic
356 blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign
357 measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median
358 changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to
359 those seen with placebo (see ADVERSE REACTIONS: Chronic Obstructive Pulmonary Disease
360 Associated With Chronic Bronchitis).

361 Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence
362 of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when
363 beta-agonists and methylxanthines are administered concurrently. The clinical significance of
364 these findings is unknown.

365 **CLINICAL TRIALS**

366 **Asthma: Adult and Adolescent Patients 12 Years of Age and Older:** In clinical trials
367 comparing ADVAIR DISKUS with the individual components, improvements in most efficacy
368 endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate
369 or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS
370 and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from
371 separate inhalers.

372 **Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or**
373 **Salmeterol Alone:** Three (3) double-blind, parallel-group clinical trials were conducted with
374 ADVAIR DISKUS in 1,208 adolescent and adult patients (≥ 12 years, baseline FEV₁ 63% to 72%
375 of predicted normal) with asthma that was not optimally controlled on their current therapy. All
376 treatments were inhalation powders, given as 1 inhalation from the DISKUS device twice daily,
377 and other maintenance therapies were discontinued.

378 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled,
379 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,
380 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to
381 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids
382 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;
383 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)
384 or salmeterol (N = 106). Baseline FEV₁ measurements were similar across treatments: ADVAIR

385 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and
386 placebo, 2.15 L.

387 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were
388 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically
389 important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN[®]
390 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency
391 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed
392 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving
393 ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone
394 propionate, salmeterol, and placebo.

395

396 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**
397 **Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

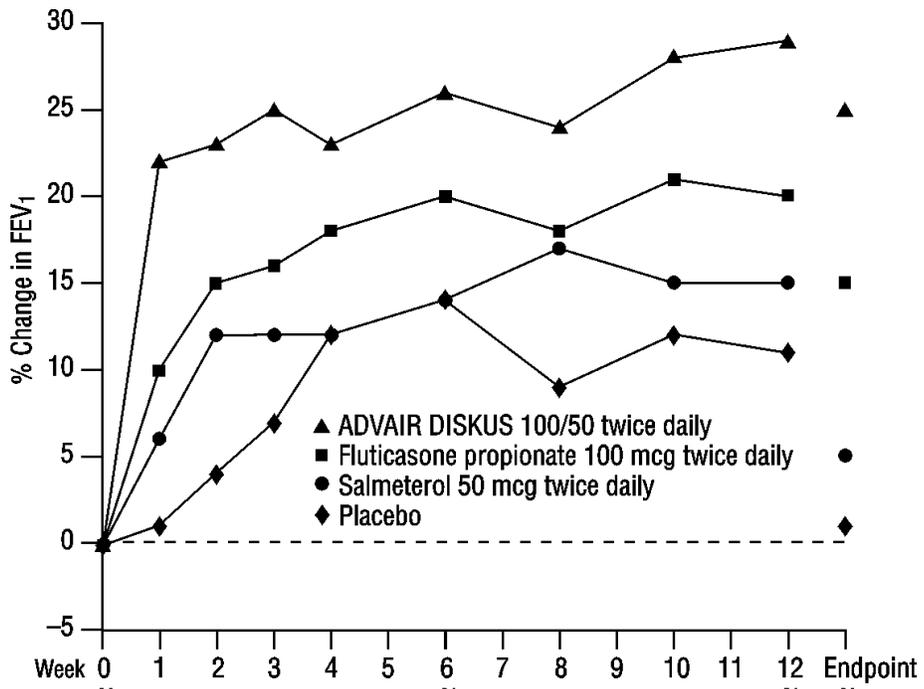
ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

398

399 The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for
400 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁
401 results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR
402 DISKUS 100/50 had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with
403 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,
404 1%). These improvements in FEV₁ with ADVAIR DISKUS were achieved regardless of baseline
405 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

406

407 **Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients With Asthma**
 408 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**
 409



	Week 0	Week 6	Week 12	Endpoint
	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 100/50	87	79	73	86
Fluticasone propionate 100 mcg	85	71	65	85
Salmeterol 50 mcg	86	59	51	86
Placebo	77	34	27	74

410
 411
 412 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in
 413 Table 2.
 414

415 **Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With**
 416 **Either Inhaled Corticosteroids or Salmeterol (Study 1)**

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

*Change from baseline = change from baseline at Endpoint (last available data).

417
 418 The subjective impact of asthma on patients' perception of health was evaluated through use
 419 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point
 420 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS
 421 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as
 422 defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores
 423 (difference in AQLQ score of 1.25 compared to placebo).

424 **Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled,
 425 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components,
 426 fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled
 427 corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to
 428 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100
 429 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS
 430 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

431 Efficacy results in this study were similar to those observed in Study 1. Patients receiving
 432 ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%)
 433 compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and
 434 placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving
 435 ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%)
 436 compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition,
 437 ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for
 438 improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also
 439 had clinically meaningful improvements in overall asthma-specific quality of life as described in
 440 Study 1 (difference in AQLQ score of 1.29 compared to placebo).

441 **Study 3: Clinical Trial With ADVAIR DISKUS 500/50:** This 28-week, non-US
 442 study compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and
 443 concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from

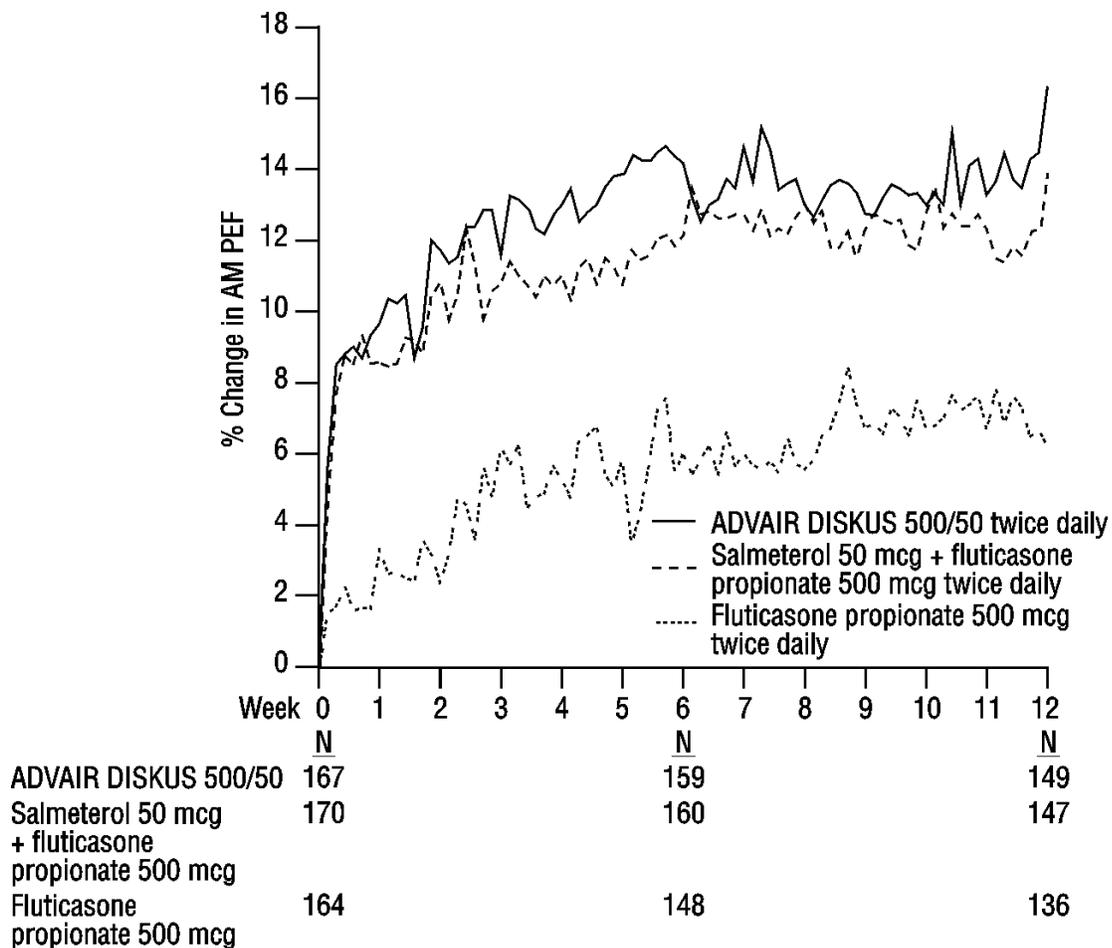
444 separate inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily
 445 doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg;
 446 flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750
 447 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected
 448 daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect
 449 safety data.

450 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,
 451 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As
 452 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50
 453 compared with fluticasone propionate 500 mcg over the 12-week treatment period.
 454 Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to
 455 improvements observed with concurrent therapy.

456

457 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory**
 458 **Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids**
 459 **(Study 3)**

460



461

462

463 **Onset of Action and Progression of Improvement in Asthma Control:** The
464 onset of action and progression of improvement in asthma control were evaluated in the 2
465 placebo-controlled US trials. Following the first dose, the median time to onset of clinically
466 significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most patients was seen within 30
467 to 60 minutes. Maximum improvement in FEV₁ generally occurred within 3 hours, and clinically
468 significant improvement was maintained for 12 hours (see Figure 3).

469 Following the initial dose, predose FEV₁ relative to Day 1 baseline improved markedly over
470 the first week of treatment and continued to improve over the 12 weeks of treatment in both
471 studies.

472 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR
473 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV₁ following
474 12 weeks of therapy.

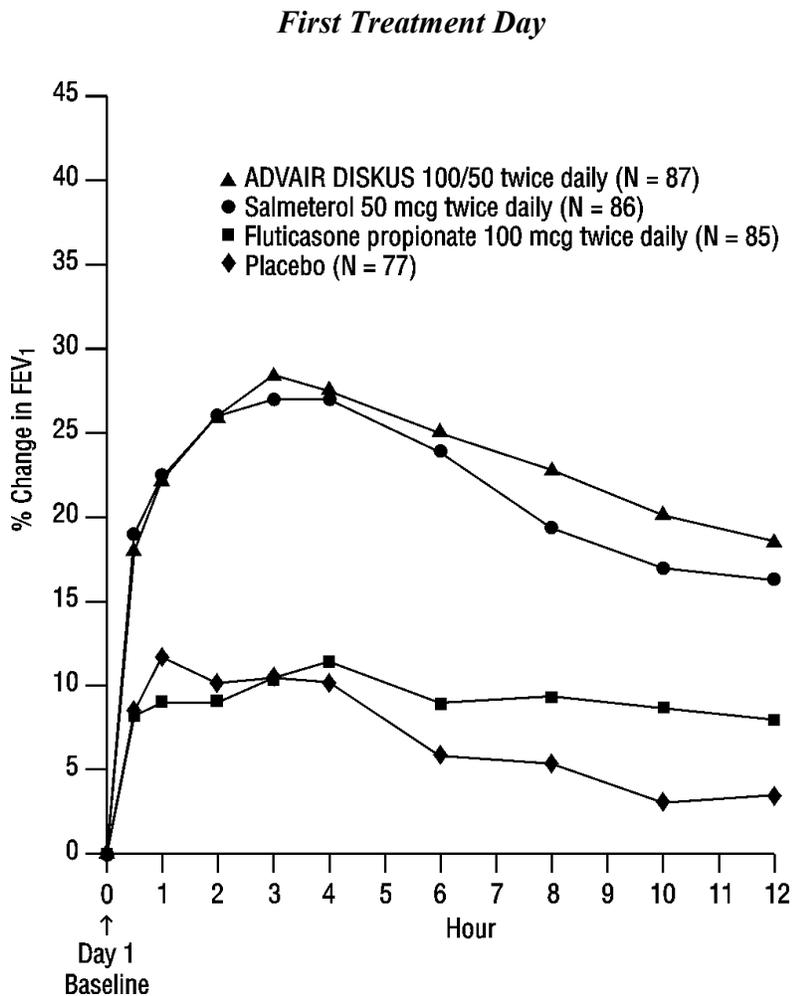
475

476 **Figure 3. Percent Change in Serial 12-hour FEV₁**
477 **in Patients With Asthma Previously Using Either Inhaled**
478 **Corticosteroids or Salmeterol (Study 1)**

479

480

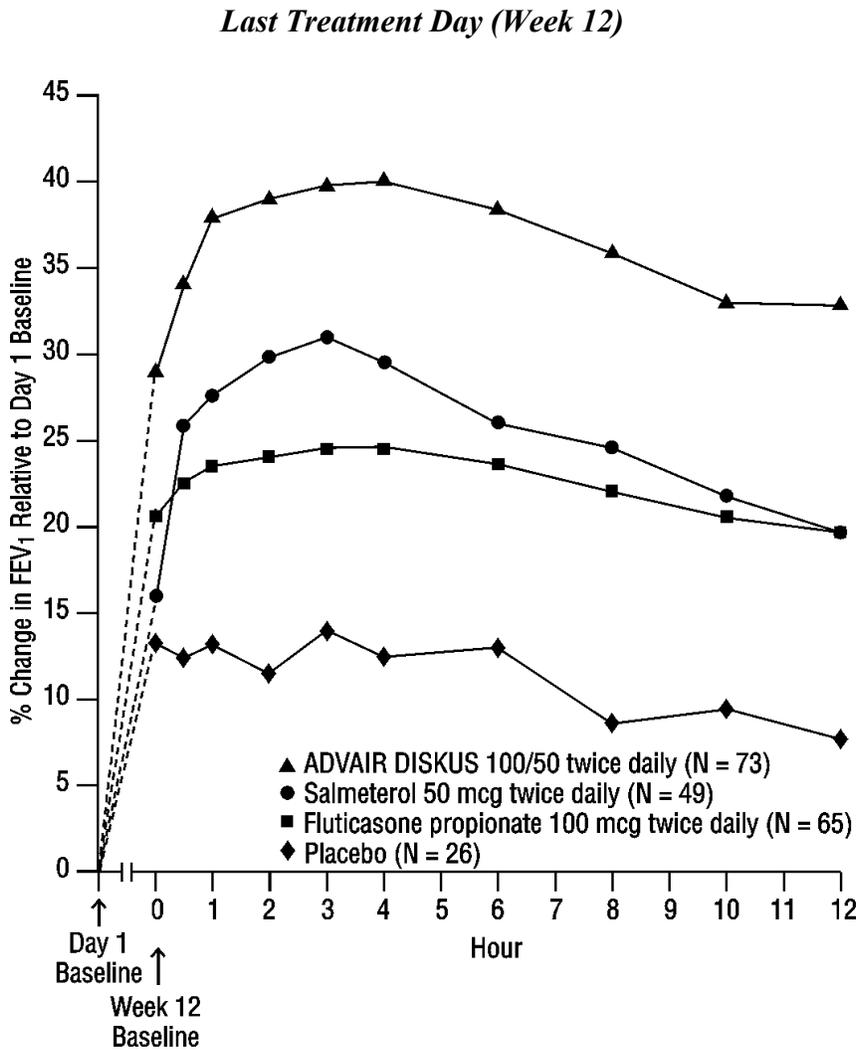
481



482

483
484
485
486
487
488
489

Figure 4. Percent Change in Serial 12-hour FEV₁ in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)



490
491

Reduction in asthma symptoms, use of rescue VENTOLIN Inhalation Aerosol, and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both studies.

Pediatric Patients: In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine

501 the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder
502 100 mcg in this age-group; however, the study also included secondary efficacy measures of
503 pulmonary function. Morning predose FEV₁ was obtained at baseline and Endpoint (last
504 available FEV₁ result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS
505 100/50, FEV₁ increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69)
506 compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in
507 patients receiving fluticasone propionate 100 mcg.

508 The findings of this study, along with extrapolation of efficacy data from patients 12 years of
509 age and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the
510 maintenance treatment of asthma in patients aged 4 to 11 years.

511 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** In a
512 clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with
513 COPD associated with chronic bronchitis, improvements in lung function (as defined by predose
514 and postdose FEV₁) were significantly greater with ADVAIR DISKUS than with fluticasone
515 propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind,
516 parallel-group, 24-week trial. All patients had a history of cough productive of sputum that was
517 not attributable to another disease process on most days for at least 3 months of the year for at
518 least 2 years. Study treatments were inhalation powders given as 1 inhalation from the DISKUS
519 device twice daily. Maintenance COPD therapies were discontinued, with the exception of
520 theophylline.

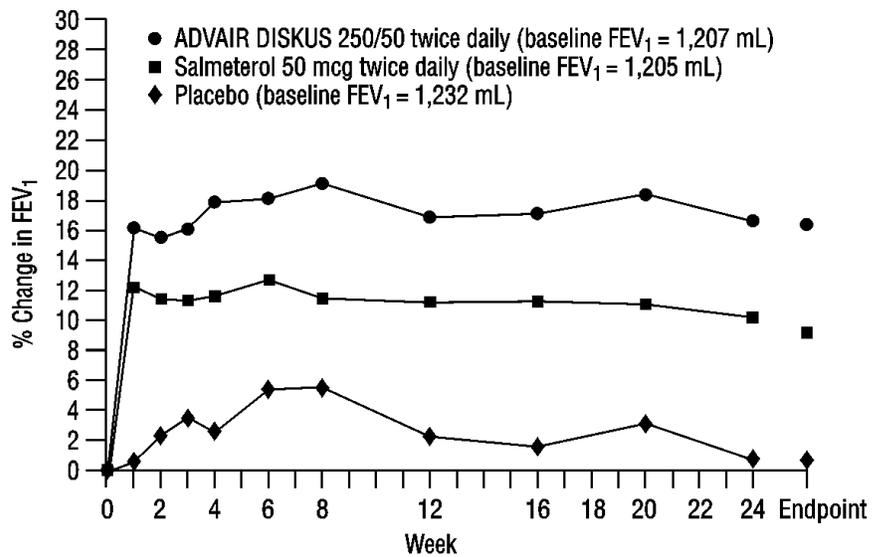
521 Figures 5 and 6 display predose and 2-hour postdose FEV₁ results. To account for patient
522 withdrawals during the study, FEV₁ at Endpoint (last evaluable FEV₁) was evaluated. Patients
523 receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV₁ at
524 Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL,
525 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung
526 function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had
527 significantly greater improvements in postdose FEV₁ at Endpoint (281 mL, 27%) compared with
528 fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the
529 contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS
530 (Figure 6).

531 A similar degree of improvement in lung function was also observed with ADVAIR DISKUS
532 500/50 twice daily.

533

534 **Figure 5. Predose FEV₁: Mean Percent Change From Baseline in Patients**
 535 **With COPD Associated With Chronic Bronchitis**

536

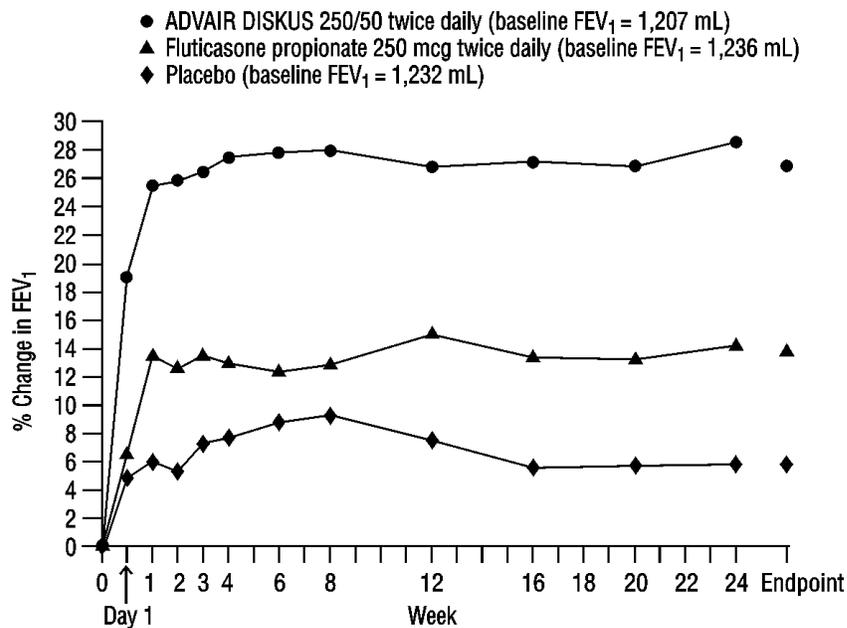


	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

537

538

539 **Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline**
 540 **Over Time in Patients With COPD Associated With Chronic Bronchitis**
 541



	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	117	171
Fluticasone propionate 250 mcg	183	147	130	175
Placebo	185	139	119	172

542
 543
 544 Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a
 545 significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis
 546 Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo
 547 over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50
 548 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of
 549 more systemic exposure to fluticasone propionate from this higher dose and no documented
 550 advantage for efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

551 The benefit of treatment of patients with COPD associated with chronic bronchitis with
 552 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated.

553 **INDICATIONS AND USAGE**

554 **Asthma:** ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment
 555 of asthma in patients 4 years of age and older.

556 ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

557 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:**

558 ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow
 559 obstruction in patients with COPD associated with chronic bronchitis.

560 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
 561 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,

562 are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive
563 Pulmonary Disease Associated With Chronic Bronchitis).

564 The benefit of treating patients with COPD associated with chronic bronchitis with ADVAIR
565 DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are
566 treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods
567 longer than 6 months should be reevaluated periodically to assess the continuing benefits and
568 potential risks of treatment.

569 ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

570 **CONTRAINDICATIONS**

571 ADVAIR DISKUS is contraindicated in the primary treatment of status asthmaticus or other
572 acute episodes of asthma or COPD where intensive measures are required.

573 Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see
574 DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site*
575 *Specific*).

576 **WARNINGS**

577 DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS
578 STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR
579 DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR
580 ASTHMA-RELATED DEATHS. Data from this study further suggest that the risk might be
581 greater in African American patients. The Salmeterol Multi-center Asthma Research Trial
582 (SMART) was a randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve
583 patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg
584 twice daily over 28 weeks compared to placebo when added to usual asthma therapy. The
585 primary endpoint was the combined number of respiratory-related deaths or respiratory-related
586 life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints
587 included combined asthma-related deaths or life-threatening experiences and asthma-related
588 deaths.

589 A planned interim analysis was conducted when approximately half of the intended number of
590 patients had been enrolled (N = 26,355). Due to the low rate of primary events in the study, the
591 findings of the planned interim analysis were not conclusive. However, analyses of secondary
592 endpoints suggested that patients receiving salmeterol may be at increased risk for some of these
593 events compared to patients receiving placebo. The analysis for the total population showed a
594 relative risk of 1.40 (95% CI 0.91, 2.14) for the primary endpoint in the salmeterol group relative
595 to the placebo group (50 out of 13,176 vs. 36 out of 13,179, respectively). In the total population,
596 a higher number of asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.25, 15.34) and combined
597 asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89)
598 occurred in patients treated with salmeterol than those treated with placebo. The analysis of the
599 African American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary
600 endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2,366

601 vs. 5 out of 2,319, respectively). In African Americans, a higher number of asthma-related deaths
602 (7 vs. 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening
603 experiences (19 vs. 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol
604 than those treated with placebo. Analysis of the Caucasian population showed a relative risk of
605 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to
606 those treated with placebo (29 out of 9,281 vs. 28 out of 9,361, respectively). In Caucasians, a
607 higher number of asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in
608 patients treated with salmeterol than in patients treated with placebo. In Caucasians, the relative
609 risk was 1.08 (17 vs. 16, 95% CI 0.55, 2.14) for combined asthma-related deaths or
610 life-threatening experiences in patients treated with salmeterol relative to placebo. The numbers
611 of patients from other ethnic groups were too small to draw any conclusions in these populations.
612 Even though SMART did not reach predetermined stopping criteria for the total population, the
613 study was stopped due to the findings in African American patients and difficulties in
614 enrollment. The data from the SMART study are not adequate to determine whether concurrent
615 use of inhaled corticosteroids, such as fluticasone propionate, a component of ADVAIR
616 DISKUS, provides protection from this risk. Therefore, it is not known whether the findings seen
617 with SEREVENT Inhalation Aerosol would apply to ADVAIR DISKUS. Given the similar basic
618 mechanisms of action of beta₂-agonists, it is possible that the findings seen in the SMART study
619 may be consistent with a class effect.

620 Findings similar to the SMART study findings were reported in a prior 16-week clinical study
621 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the
622 SNS study, the incidence of asthma-related death was numerically, though not statistically,
623 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol
624 (180 mcg 4 times daily) added to usual asthma therapy.

625 **1. ADVAIR DISKUS SHOULD NOT BE USED FOR TRANSFERRING PATIENTS**
626 **FROM SYSTEMIC CORTICOSTEROID THERAPY.** Particular care is needed for patients
627 who have been transferred from systemically active corticosteroids to inhaled corticosteroids
628 because deaths due to adrenal insufficiency have occurred in patients with asthma during and
629 after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.
630 After withdrawal from systemic corticosteroids, a number of months are required for recovery of
631 HPA function.

632 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its
633 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been
634 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs
635 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection
636 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although
637 inhaled corticosteroids may provide control of asthma symptoms during these episodes, in
638 recommended doses they supply less than normal physiological amounts of glucocorticoid
639 systemically and do NOT provide the mineralocorticoid activity that is necessary for coping with
640 these emergencies.

641 During periods of stress or a severe asthma attack, patients who have been withdrawn from
642 systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses)
643 immediately and to contact their physicians for further instruction. These patients should also be
644 instructed to carry a warning card indicating that they may need supplementary systemic
645 corticosteroids during periods of stress or a severe asthma attack.

646 **2. ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY**
647 **DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF**
648 **ASTHMA. Serious acute respiratory events, including fatalities, have been reported both in**
649 **the United States and worldwide when salmeterol, a component of ADVAIR DISKUS, has**
650 **been initiated in patients with significantly worsening or acutely deteriorating asthma. In**
651 most cases, these have occurred in patients with severe asthma (e.g., patients with a history of
652 corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent
653 hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients
654 in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications;
655 increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic
656 corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or
657 progressive deterioration in pulmonary function). However, they have occurred in a few patients
658 with less severe asthma as well. It was not possible from these reports to determine whether
659 salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

660 **3. Drug Interaction With Ritonavir:** A drug interaction study in healthy subjects has shown
661 that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma
662 fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations
663 (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug*
664 *Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During
665 postmarketing use, there have been reports of clinically significant drug interactions in patients
666 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects
667 including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone
668 propionate and ritonavir is not recommended unless the potential benefit to the patient
669 outweighs the risk of systemic corticosteroid side effects.

670 **4. Do Not Use ADVAIR DISKUS to Treat Acute Symptoms:** An inhaled, short-acting
671 beta₂-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of
672 breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an
673 inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of shortness of breath that
674 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

675 When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or
676 inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to
677 discontinue the regular use of these drugs. For patients taking ADVAIR DISKUS, inhaled,
678 short-acting beta₂-agonists should only be used for symptomatic relief of acute symptoms of
679 shortness of breath (see PRECAUTIONS: Information for Patients).

680 5. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of
681 Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically over
682 several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective,
683 the patient needs more inhalations than usual, or the patient develops a significant decrease in
684 lung function, this may be a marker of destabilization of the disease. In this setting, the patient
685 requires immediate reevaluation with reassessment of the treatment regimen, giving special
686 consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a
687 higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids.
688 Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR
689 DISKUS.

690 6. Do Not Use an Inhaled, Long-Acting Beta₂-Agonist in Conjunction With ADVAIR DISKUS:
691 Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol
692 or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of exercise-induced
693 bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of
694 bronchospasm associated with COPD. Additional benefit would not be gained from using
695 supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already
696 contains an inhaled, long-acting beta₂-agonist.

697 7. Do Not Exceed Recommended Dosage: ADVAIR DISKUS should not be used more often or
698 at higher doses than recommended. Fatalities have been reported in association with excessive
699 use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times
700 the recommended dose) have been associated with clinically significant prolongation of the QTc
701 interval, which has the potential for producing ventricular arrhythmias.

702 8. Paradoxical Bronchospasm: As with other inhaled asthma and COPD medications, ADVAIR
703 DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical
704 bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated
705 immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be
706 discontinued immediately, and alternative therapy should be instituted.

707 9. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after
708 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash,
709 and bronchospasm.

710 10. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as
711 stridor and choking, have been reported in patients receiving fluticasone propionate and
712 salmeterol, components of ADVAIR DISKUS.

713 11. Cardiovascular Disorders: ADVAIR DISKUS, like all products containing sympathomimetic
714 amines, should be used with caution in patients with cardiovascular disorders, especially
715 coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of
716 ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as
717 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon
718 after administration of salmeterol at recommended doses, if they occur, the drug may need to be
719 discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as

720 flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The
721 clinical significance of these findings is unknown.

722 12. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic
723 corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by
724 the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and
725 eosinophilic conditions.

726 13. Immunosuppression: Persons who are using drugs that suppress the immune system are more
727 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can
728 have a more serious or even fatal course in susceptible children or adults using corticosteroids.
729 In such children or adults who have not had these diseases or been properly immunized,
730 particular care should be taken to avoid exposure. How the dose, route, and duration of
731 corticosteroid administration affect the risk of developing a disseminated infection is not known.
732 The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also
733 not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)
734 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular
735 immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG
736 and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be
737 considered.

738 **PRECAUTIONS**

739 **General: Cardiovascular Effects:** Cardiovascular and central nervous system effects seen
740 with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can
741 occur after use of salmeterol, a component of ADVAIR DISKUS, and may require
742 discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing
743 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,
744 especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with
745 convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to
746 sympathomimetic amines.

747 As has been described with other beta-adrenergic agonist bronchodilators, clinically
748 significant changes in electrocardiograms (ECGs) have been seen infrequently in individual
749 patients in controlled clinical studies with ADVAIR DISKUS and salmeterol. Clinically
750 significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen
751 infrequently in individual patients in controlled clinical studies with salmeterol, a component of
752 ADVAIR DISKUS.

753 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may affect
754 normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of
755 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving
756 chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice
757 daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and
758 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar

759 region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the
760 COPD population have not been studied.

761 In patients with major risk factors for decreased bone mineral content, such as tobacco use,
762 advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of
763 drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS
764 may pose an additional risk. Since patients with COPD often have multiple risk factors for
765 reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR
766 DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and
767 ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD
768 therapy, use of medication to treat or prevent osteoporosis should be strongly considered.
769 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
770 COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS
771 500/50, are not recommended.

772 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with
773 asthma and COPD following the long-term administration of inhaled corticosteroids, including
774 fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations
775 should be considered.

776 Lower respiratory tract infections, including pneumonia, have been reported following the
777 inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR
778 DISKUS.

779 Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously,
780 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic
781 agonist medications may produce significant hypokalemia in some patients, possibly through
782 intracellular shunting, which has the potential to produce adverse cardiovascular effects. The
783 decrease in serum potassium is usually transient, not requiring supplementation.

784 Clinically significant changes in blood glucose and/or serum potassium were seen
785 infrequently during clinical studies with ADVAIR DISKUS at recommended doses.

786 During withdrawal from oral corticosteroids, some patients may experience symptoms of
787 systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and
788 depression, despite maintenance or even improvement of respiratory function.

789 Fluticasone propionate, a component of ADVAIR DISKUS, will often help control asthma
790 symptoms with less suppression of HPA function than therapeutically equivalent oral doses of
791 prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically
792 active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing HPA
793 dysfunction may be expected only when recommended dosages are not exceeded and individual
794 patients are titrated to the lowest effective dose. A relationship between plasma levels of
795 fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown
796 after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual
797 sensitivity to effects on cortisol production exists, physicians should consider this information
798 when prescribing ADVAIR DISKUS.

799 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated
800 with ADVAIR DISKUS should be observed carefully for any evidence of systemic
801 corticosteroid effects. Particular care should be taken in observing patients postoperatively or
802 during periods of stress for evidence of inadequate adrenal response.

803 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal
804 suppression (including adrenal crisis) may appear in a small number of patients, particularly
805 when fluticasone propionate is administered at higher than recommended doses over prolonged
806 periods of time. If such effects occur, the dosage of ADVAIR DISKUS should be reduced
807 slowly, consistent with accepted procedures for reducing systemic corticosteroids and for
808 management of asthma symptoms.

809 A reduction of growth velocity in children and adolescents may occur as a result of poorly
810 controlled asthma or from the therapeutic use of corticosteroids, including inhaled
811 corticosteroids. The effects of long-term treatment of children and adolescents with inhaled
812 corticosteroids, including fluticasone propionate, on final adult height are not known.

813 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone
814 propionate inhalation powder (FLOVENT[®] ROTADISK[®]) at 50 and 100 mcg twice daily was
815 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to
816 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were
817 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and
818 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering
819 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled
820 asthma may be confounding factors in interpreting these data. A separate subset analysis of
821 children who remained prepubertal during the study revealed growth rates at 52 weeks of
822 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and
823 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of
824 children in this study, the range for expected growth velocity is: boys – 3rd
825 percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls –
826 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

827 The clinical significance of these growth data is not certain. Physicians should closely follow
828 the growth of children and adolescents taking corticosteroids by any route, and weigh the
829 benefits of corticosteroid therapy against the possibility of growth suppression if growth appears
830 slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that
831 effectively controls their asthma.

832 The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In
833 particular, the effects resulting from chronic use of fluticasone propionate on developmental or
834 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients
835 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or
836 longer. In clinical studies in patients with asthma treated for 2 years with inhaled fluticasone
837 propionate, no apparent differences in the type or severity of adverse reactions were observed
838 after long- versus short-term treatment.

839 In clinical studies with ADVAIR DISKUS, the development of localized infections of the
840 pharynx with *Candida albicans* has occurred. When such an infection develops, it should be
841 treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on
842 treatment with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be
843 interrupted.

844 Inhaled corticosteroids should be used with caution, if at all, in patients with active or
845 quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial,
846 viral, or parasitic infections; or ocular herpes simplex.

847 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
848 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some
849 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
850 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
851 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
852 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
853 have also been reported with other inhaled corticosteroids in this clinical setting. Physicians
854 should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac
855 complications, and/or neuropathy presenting in their patients. A causal relationship between
856 fluticasone propionate and these underlying conditions has not been established (see ADVERSE
857 REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

858 **Chronic Obstructive Pulmonary Disease:** ADVAIR DISKUS 250/50 twice daily is the
859 only dosage recommended for the treatment of airflow obstruction in patients with COPD
860 associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not
861 recommended, as no additional improvement in lung function (defined by predose and postdose
862 FEV₁) was observed in clinical trials and higher doses of corticosteroids increase the risk of
863 systemic effects.

864 The benefit of treatment of patients with COPD associated with chronic bronchitis with
865 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients
866 who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis
867 for periods longer than 6 months should be reevaluated periodically to assess the continuing
868 benefits and potential risks of treatment.

869 **Information for Patients:** Patients being treated with ADVAIR DISKUS should receive the
870 following information and instructions. This information is intended to aid them in the safe and
871 effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

872 It is important that patients understand how to use the DISKUS inhalation device
873 appropriately and how it should be used in relation to other asthma or COPD medications they
874 are taking. Patients should be given the following information:

- 875 1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical
876 trials indicate significant improvement may occur within the first 30 minutes of taking the
877 first dose; however, the full benefit may not be achieved until treatment has been
878 administered for 1 week or longer. The patient should not use more than the prescribed

- 879 dosage but should contact the physician if symptoms do not improve or if the condition
880 worsens.
- 881 2. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,
882 whether or not patients are able to sense delivery of a dose, you should instruct them not to
883 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12
884 hours apart. You should instruct them to contact you or the pharmacist if they have questions.
- 885 3. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or
886 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not
887 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use
888 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of
889 EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in
890 COPD.
- 891 4. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should
892 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting
893 beta₂-agonist such as albuterol (the physician should provide the patient with such
894 medication and instruct the patient in how it should be used). ADVAIR DISKUS is not
895 meant to relieve acute asthma symptoms or exacerbations of COPD.
- 896 5. Patients should not stop therapy with ADVAIR DISKUS without physician/provider
897 guidance since symptoms may recur after discontinuation.
- 898 6. The physician should be notified immediately if any of the following situations occur, which
899 may be a sign of seriously worsening asthma:
- 900 • decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - 901 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - 902 • significant decrease in lung function as outlined by the physician.
- 903 7. Patients should be cautioned regarding common adverse effects associated with
904 beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 905 8. Patients who are at an increased risk for decreased BMD should be advised that the use of
906 corticosteroids may pose an additional risk and should be told to monitor and, where
907 appropriate, seek treatment for this condition.
- 908 9. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
909 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).
910 Regular eye examinations should be considered.
- 911 10. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD
912 should be used only as directed by their physicians.
- 913 11. ADVAIR DISKUS should not be used with a spacer device.
- 914 12. Patients who are pregnant or nursing should contact their physicians about the use of
915 ADVAIR DISKUS.
- 916 13. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it
917 should be used:
- 918 • Never exhale into the DISKUS.

- 919 • Never attempt to take the DISKUS apart.
920 • Always activate and use the DISKUS in a level, horizontal position.
921 • After inhalation, rinse the mouth with water without swallowing.
922 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
923 • Always keep the DISKUS in a dry place.
924 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after
925 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
926 14. Patients should be warned to avoid exposure to chickenpox or measles and, if they are
927 exposed, to consult their physicians without delay.
928 15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient
929 should read and carefully follow the Patient’s Instructions for Use accompanying the
930 product.

931 **Drug Interactions:** ADVAIR DISKUS has been used concomitantly with other drugs,
932 including short-acting beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly
933 used in patients with asthma or COPD, without adverse drug reactions. No formal drug
934 interaction studies have been performed with ADVAIR DISKUS.

935 **Short-Acting Beta₂-Agonists:** In clinical trials with patients with asthma, the mean daily
936 need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR
937 DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five
938 percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations
939 per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse
940 reactions was observed among patients who averaged 6 or more inhalations per day.

941 In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR
942 DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR
943 DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No
944 increase in frequency of cardiovascular adverse reactions was observed among patients who
945 averaged 6 or more inhalations of albuterol per day.

946 **Methylxanthines:** The concurrent use of intravenously or orally administered
947 methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of
948 age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials
949 with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50
950 twice daily concurrently with a theophylline product had adverse event rates similar to those in
951 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in
952 patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily
953 concurrently with a theophylline product (N = 39) or without theophylline (N = 132).

954 In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily
955 concurrently with a theophylline product had adverse event rates similar to those in 161 patients
956 receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant
957 administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse
958 event profile.

959 **Fluticasone Propionate Nasal Spray:** In adult and adolescent patients 12 years of age
960 and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse
961 events or HPA axis effects was noted between patients taking FLONASE[®] (fluticasone
962 propionate) Nasal Spray, 50 mcg concurrently (N = 46) and those who were not (N = 130).

963 **Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** ADVAIR DISKUS
964 should be administered with extreme caution to patients being treated with monoamine oxidase
965 inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents,
966 because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system
967 may be potentiated by these agents.

968 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the
969 pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but
970 may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma
971 should not normally be treated with beta-blockers. However, under certain circumstances, there
972 may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with
973 asthma. In this setting, cardioselective beta-blockers could be considered, although they should
974 be administered with caution.

975 **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of
976 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by
977 beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although
978 the clinical significance of these effects is not known, caution is advised in the coadministration
979 of beta-agonists with nonpotassium-sparing diuretics.

980 **Inhibitors of Cytochrome P450:** Fluticasone propionate is a substrate of cytochrome
981 P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy
982 subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can
983 significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced
984 serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics:
985 *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports
986 of clinically significant drug interactions in patients receiving fluticasone propionate and
987 ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal
988 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not
989 recommended unless the potential benefit to the patient outweighs the risk of systemic
990 corticosteroid side effects.

991 In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a
992 single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of
993 ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate
994 exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.
995 Caution should be exercised when ADVAIR DISKUS is coadministered with ketoconazole and
996 other known potent cytochrome P450 3A4 inhibitors.

997 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**
998 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to

999 1,000 mcg/kg (approximately 4 and 10 times, respectively, the maximum recommended daily
1000 inhalation dose in adults and children on a mcg/m² basis) for 78 weeks or in rats at inhalation
1001 doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum
1002 recommended daily inhalation dose in adults and children on a mcg/m² basis) for 104 weeks.

1003 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in
1004 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in
1005 vitro or in the mouse micronucleus test.

1006 No evidence of impairment of fertility was observed in reproductive studies conducted in
1007 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum
1008 recommended daily inhalation dose in adults on a mcg/m² basis). Prostate weight was
1009 significantly reduced at a subcutaneous dose of 50 mcg/kg.

1010 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of
1011 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose
1012 in adults and children based on comparison of the plasma area under the curves [AUCs]) caused
1013 a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular
1014 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of
1015 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg
1016 (approximately 3 times the maximum recommended daily inhalation doses in adults and children
1017 based on comparison of the AUCs).

1018 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol
1019 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at
1020 doses of 0.68 mg/kg and above (approximately 55 and 25 times, respectively, the maximum
1021 recommended daily inhalation dose in adults and children on a mg/m² basis). No tumors were
1022 seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended
1023 daily inhalation dose in adults and children on a mg/m² basis). These findings in rodents are
1024 similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of
1025 these findings to human use is unknown.

1026 Salmeterol produced no detectable or reproducible increases in microbial and mammalian
1027 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
1028 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated
1029 with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum
1030 recommended daily inhalation dose in adults on a mg/m² basis).

1031 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the
1032 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using
1033 combinations of fluticasone propionate and salmeterol compared to toxicity data from the
1034 components administered separately. In mice combining 150 mcg/kg subcutaneously of
1035 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a
1036 mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum
1037 recommended daily inhalation dose in adults on a mg/m² basis) was teratogenic. Cleft palate,
1038 fetal death, increased implantation loss and delayed ossification were seen. These observations

1039 are characteristic of glucocorticoids. No developmental toxicity was observed at combination
1040 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum
1041 recommended daily inhalation dose in adults on a mcg/m² basis) and up to 1.4 mg/kg orally of
1042 salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults
1043 on a mg/m² basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg
1044 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation
1045 dose in adults on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 80 times the
1046 maximum recommended daily inhalation dose in adults on a mg/m² basis). Combining
1047 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended
1048 daily inhalation dose in adults on a mcg/m² basis) with 10 mg/kg orally of salmeterol
1049 (approximately 810 times the maximum recommended daily inhalation dose in adults on a
1050 mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,
1051 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate
1052 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS
1053 should be used during pregnancy only if the potential benefit justifies the potential risk to the
1054 fetus.

1055 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse
1056 and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily
1057 inhalation dose in adults on a mcg/m² basis), respectively, revealed fetal toxicity characteristic of
1058 potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft
1059 palate, and retarded cranial ossification.

1060 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
1061 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m²
1062 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
1063 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m²
1064 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
1065 study, consistent with the established low bioavailability following oral administration (see
1066 CLINICAL PHARMACOLOGY).

1067 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
1068 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a
1069 mcg/m² basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats
1070 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a
1071 mcg/m² basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5
1072 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

1073 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate
1074 should be used during pregnancy only if the potential benefit justifies the potential risk to the
1075 fetus.

1076 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to
1077 physiologic, doses suggests that rodents are more prone to teratogenic effects from
1078 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid

1079 production during pregnancy, most women will require a lower exogenous corticosteroid dose
1080 and many will not need corticosteroid treatment during pregnancy.

1081 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses
1082 up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in
1083 adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and
1084 above (approximately 50 times the maximum recommended daily inhalation dose in adults based
1085 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting
1086 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,
1087 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.
1088 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the
1089 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

1090 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal
1091 bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum
1092 recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other
1093 beta-agonists has provided no evidence that these class effects in animals are relevant to their use
1094 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant
1095 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the
1096 potential risk to the fetus.

1097 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice
1098 and rats (approximately 410 and 810 times, respectively, the maximum recommended daily
1099 inhalation dose in adults on a mg/m² basis).

1100 **Use in Labor and Delivery:** There are no well-controlled human studies that have
1101 investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the
1102 potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during
1103 labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

1104 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after
1105 inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There
1106 are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known
1107 whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast
1108 milk. However, other corticosteroids have been detected in human milk. Subcutaneous
1109 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the
1110 maximum recommended daily inhalation dose in adults on a mcg/m² basis) resulted in
1111 measurable radioactivity in milk.

1112 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing
1113 mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR
1114 DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

1115 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

1116 **Pediatric Use:** Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported
1117 by extrapolation of efficacy data from older patients and by safety and efficacy data from a study
1118 of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL

1119 TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric*
1120 *Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under
1121 4 years of age have not been established.

1122 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a
1123 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of
1124 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive
1125 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used
1126 tests of HPA axis function. The long-term effects of this reduction in growth velocity associated
1127 with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The
1128 potential for “catch-up” growth following discontinuation of treatment with orally inhaled
1129 corticosteroids has not been adequately studied.

1130 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,
1131 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS:
1132 *General: Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled
1133 corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on
1134 any corticosteroid appears to have growth suppression, the possibility that he/she is particularly
1135 sensitive to this effect of corticosteroids should be considered. The potential growth effects of
1136 prolonged treatment should be weighed against the clinical benefits obtained. To minimize the
1137 systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient
1138 should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE
1139 AND ADMINISTRATION: Asthma).

1140 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS for
1141 asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total
1142 number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years
1143 of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in
1144 safety were observed between these patients and younger patients, and other reported clinical
1145 experience, including studies of the individual components, has not identified differences in
1146 responses between the elderly and younger patients, but greater sensitivity of some older
1147 individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution
1148 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant
1149 cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available
1150 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR
1151 DISKUS in geriatric patients is warranted.

1152 **ADVERSE REACTIONS**

1153 **Asthma: Adult and Adolescent Patients 12 Years of Age and Older:** The incidence of
1154 common adverse events in Table 3 is based upon 2 placebo-controlled, 12-week, US clinical
1155 studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356
1156 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with

1157 ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder
 1158 (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.

1159

1160 **Table 3. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials**
 1161 **With ADVAIR DISKUS in Patients With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, & throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal Infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3
Average duration of exposure (days)	77.3	78.7	72.4	70.1	60.1	42.3

1162

1163 Table 3 includes all events (whether considered drug-related or nondrug-related by the
1164 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR
1165 DISKUS and were more common than in the placebo group. In considering these data,
1166 differences in average duration of exposure should be taken into account. Rare cases of
1167 immediate and delayed hypersensitivity reactions, including rash and other rare events of
1168 angioedema and bronchospasm, have been reported.

1169 These adverse reactions were mostly mild to moderate in severity.

1170 Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies
1171 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1172 **Blood and Lymphatic:** Lymphatic signs and symptoms.

1173 **Cardiovascular:** Palpitations.

1174 **Drug Interaction, Overdose, and Trauma:** Muscle injuries, fractures, wounds and
1175 lacerations, contusions and hematomas, burns.

1176 **Ear, Nose, and Throat:** Rhinorrhea/postnasal drip; ear, nose, and throat infections; ear
1177 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal
1178 irritation; blood in nasal mucosa.

1179 **Eye:** Keratitis and conjunctivitis, viral eye infections, eye redness.

1180 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,
1181 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral
1182 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

1183 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1184 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower respiratory
1185 infections.

1186 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle stiffness, tightness, and
1187 rigidity; bone and cartilage disorders.

1188 **Neurology:** Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

1189 **Non-Site Specific:** Allergies and allergic reactions, congestion, viral infections, pain, chest
1190 symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

1191 **Skin:** Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of
1192 sweat and sebum, sweating.

1193 The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical
1194 study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily
1195 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and
1196 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation
1197 powder 500 mcg was similar to the incidences reported in Table 3.

1198 **Pediatric Patients: Pediatric Study:** ADVAIR DISKUS 100/50 was well tolerated in
1199 clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common
1200 adverse events in Table 4 is based upon a 12-week US study in 203 patients with asthma aged 4
1201 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry

1202 and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation
 1203 powder 100 mcg twice daily.

1204

1205 **Table 4. Overall Adverse Events With $\geq 3\%$ Incidence With ADVAIR DISKUS 100/50**
 1206 **in Patients 4 to 11 Years of Age With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 101) %	Fluticasone Propionate 100 mcg (N = 102) %
Ear, nose, & throat		
Upper respiratory tract infection	10	17
Throat irritation	8	7
Ear, nose, & throat infections	4	<1
Epistaxis	4	<1
Pharyngitis/throat infection	3	2
Ear signs & symptoms	3	<1
Sinusitis	3	0
Neurology		
Headache	20	20
Gastrointestinal		
Gastrointestinal discomfort & pain	7	5
Nausea & vomiting	5	3
Candidiasis mouth/throat	4	<1
Non-site specific		
Fever	5	13
Chest symptoms	3	<1
Average duration of exposure (days)	74.8	78.8

1207

1208 Table 4 includes all events (whether considered drug-related or nondrug-related by the
 1209 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS
 1210 100/50.

1211 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
 1212 incidence of common adverse events in Table 5 is based upon 1 placebo-controlled, 24-week, US
 1213 clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult
 1214 patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50,
 1215 fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or
 1216 placebo.

1217

1218 **Table 5. Overall Adverse Events With $\geq 3\%$ Incidence With ADVAIR DISKUS 250/50**
 1219 **in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic**
 1220 **Bronchitis**

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, & throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1
Average duration of exposure (days)	141.3	138.5	136.1	131.6

1221
 1222 Table 5 includes all events (whether considered drug-related or nondrug-related by the
 1223 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS
 1224 250/50 and were more common than in the placebo group.

1225 These adverse reactions were mostly mild to moderate in severity.

1226 Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an
 1227 incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1228 **Cardiovascular:** Syncope.

1229 **Drug Interaction, Overdose, and Trauma:** Postoperative complications.

1230 **Ear, Nose, and Throat:** Ear, nose, and throat infections; ear signs and symptoms;
 1231 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

1232 **Endocrine and Metabolic:** Hypothyroidism.

1233 **Eye:** Dry eyes, eye infections.

1234 **Gastrointestinal:** Constipation, gastrointestinal signs and symptoms, oral lesions.

1235 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1236 **Lower Respiratory:** Breathing disorders, lower respiratory signs and symptoms.
1237 **Non-Site Specific:** Bacterial infections, candidiasis unspecified site, edema and swelling,
1238 nonspecific conditions, viral infections.
1239 **Psychiatry:** Situational disorders.
1240 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
1241 trials, the following events have been identified during worldwide use of any formulation of
1242 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are
1243 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
1244 These events have been chosen for inclusion due to either their seriousness, frequency of
1245 reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol
1246 or a combination of these factors.
1247 In extensive US and worldwide postmarketing experience with salmeterol, a component of
1248 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have
1249 been reported. In most cases, these have occurred in patients with severe asthma and/or in some
1250 patients in whom asthma has been acutely deteriorating (see WARNINGS no. 2), but they have
1251 also occurred in a few patients with less severe asthma. It was not possible from these reports to
1252 determine whether salmeterol contributed to these events or simply failed to relieve the
1253 deteriorating asthma.
1254 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular
1255 tachycardia), ventricular tachycardia.
1256 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus
1257 pain, throat soreness.
1258 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity
1259 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.
1260 **Eye:** Cataracts, glaucoma.
1261 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.
1262 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.
1263 **Neurology:** Paresthesia, restlessness.
1264 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare
1265 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk
1266 protein allergy.
1267 **Psychiatry:** Agitation, aggression, depression.
1268 **Respiratory:** Chest congestion; chest tightness; dyspnea; immediate bronchospasm;
1269 influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory
1270 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.
1271 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.
1272 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal
1273 candidiasis, vaginitis, vulvovaginitis.
1274 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
1275 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some

1276 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
1277 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
1278 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
1279 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
1280 have also been reported with other inhaled corticosteroids in this clinical setting. While
1281 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid
1282 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary
1283 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal
1284 relationship between fluticasone propionate and these underlying conditions has not been
1285 established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

1286 **OVERDOSAGE**

1287 **ADVAIR DISKUS:** No deaths occurred in rats given an inhaled single-dose combination of
1288 salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum
1289 recommended daily inhalation dose in adults and children on a mg/m² basis) and 1.9 mg/kg of
1290 fluticasone propionate (approximately 15 and 35 times, respectively, the maximum
1291 recommended daily inhalation dose in adults and children on a mg/m² basis).

1292 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in
1293 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other*
1294 *Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate
1295 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation
1296 aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of
1297 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.
1298 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to
1299 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or
1300 moderate severity, and incidences were similar in active and placebo treatment groups. In mice,
1301 the oral median lethal dose was >1,000 mg/kg (>4,100 and >9,600 times, respectively, the
1302 maximum recommended daily inhalation dose in adults and children on a mg/m² basis). In rats
1303 the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times,
1304 respectively, the maximum recommended daily inhalation dose in adults and children on a
1305 mg/m² basis).

1306 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of
1307 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
1308 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
1309 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,
1310 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and
1311 insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the
1312 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia
1313 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead

1314 to clinically significant prolongation of the QTc interval, which can produce ventricular
1315 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.
1316 As with all sympathomimetic medications, cardiac arrest and even death may be associated
1317 with abuse of salmeterol.

1318 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic
1319 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing
1320 in mind that such medication can produce bronchospasm. There is insufficient evidence to
1321 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is
1322 recommended in cases of overdosage.

1323 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg
1324 (approximately 240 and 110 times, respectively, the maximum recommended daily inhalation
1325 dose in adults and children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg
1326 (approximately 190 and 90 times, respectively, the maximum recommended daily inhalation
1327 dose in adults and children on a mg/m² basis). By the oral route, no deaths occurred in mice at
1328 150 mg/kg (approximately 6,100 and 2,900 times, respectively, the maximum recommended
1329 daily inhalation dose in adults and children on a mg/m² basis) and in rats at 1,000 mg/kg
1330 (approximately 81,000 and 38,000 times, respectively, the maximum recommended daily
1331 inhalation dose in adults and children on a mg/m² basis).

1332 **DOSAGE AND ADMINISTRATION**

1333 ADVAIR DISKUS should be administered by the orally inhaled route only (see Patient's
1334 Instructions for Use). After inhalation, the patient should rinse the mouth with water without
1335 swallowing. ADVAIR DISKUS should not be used for transferring patients from systemic
1336 corticosteroid therapy.

1337 **Asthma:** ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR
1338 DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of
1339 fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

1340 ADVAIR DISKUS should be administered twice daily every day. More frequent
1341 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation
1342 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some
1343 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety
1344 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not
1345 been established.

1346 If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should
1347 be taken for immediate relief.

1348 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
1349 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB,
1350 or for any other reason.

1351 **Adult and Adolescent Patients 12 Years of Age and Older:** For patients 12 years of
 1352 age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately
 1353 12 hours apart).

1354 The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and
 1355 older are based upon patients' current asthma therapy.

- 1356 • For patients who are not currently on an inhaled corticosteroid, whose disease severity
 1357 warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid
 1358 maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice
 1359 daily.
- 1360 • For patients on an inhaled corticosteroid, Table 6 provides the recommended starting dosage.
 1361 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1362 **For all patients it is desirable to titrate to the lowest effective strength after adequate**
 1363 **asthma stability is achieved.**

1364

1365 **Table 6. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged 12**
 1366 **Years and Older Taking Inhaled Corticosteroids**

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate	≤420 mcg	100/50 twice daily
	462-840 mcg	250/50 twice daily
Budesonide	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Fluticasone propionate inhalation aerosol	≤176 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	660-880 mcg*	500/50 twice daily
Fluticasone propionate inhalation powder	≤200 mcg	100/50 twice daily
	500 mcg	250/50 twice daily
	1,000 mcg*	500/50 twice daily
Triamcinolone acetonide	≤1,000 mcg	100/50 twice daily
	1,100-1,600 mcg	250/50 twice daily

* ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

1367

1368 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can
 1369 occur within 30 minutes of beginning treatment, although maximum benefit may not be

1370 achieved for 1 week or longer after starting treatment. Individual patients will experience a
1371 variable time to onset and degree of symptom relief.

1372 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,
1373 replacing the current strength of ADVAIR DISKUS with a higher strength may provide
1374 additional improvement in asthma control.

1375 If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate
1376 improvement in asthma control, the therapeutic regimen should be reevaluated and additional
1377 therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher
1378 strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be
1379 considered.

1380 **Pediatric Patients:** For patients aged 4 to 11 years who are symptomatic on an inhaled
1381 corticosteroid the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and
1382 evening, approximately 12 hours apart).

1383 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
1384 dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately
1385 12 hours apart).

1386 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
1387 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,
1388 are not recommended, as no additional improvement in lung function was observed in clinical
1389 trials and higher doses of corticosteroids increase the risk of systemic effects.

1390 If shortness of breath occurs in the period between doses, an inhaled, short-acting
1391 beta₂-agonist should be taken for immediate relief.

1392 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
1393 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for the maintenance
1394 treatment of COPD or for any other reason.

1395 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see
1396 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety
1397 did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and
1398 its active components, no dosage adjustment is recommended.

1399 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of
1400 ADVAIR DISKUS.

1401 **HOW SUPPLIED**

1402 ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters.
1403 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1404 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional
1405 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1406 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1407 (NDC 0173-0695-02).

1408 ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters.
1409 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1410 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional
1411 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1412 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1413 (NDC 0173-0696-02).

1414 ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters.
1415 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1416 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional
1417 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1418 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1419 (NDC 0173-0697-02).

1420 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place**
1421 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**
1422 **device is not reusable. The device should be discarded 1 month after removal from the**
1423 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**
1424 **indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**

1425
1426



1427
1428 GlaxoSmithKline
1429 Research Triangle Park, NC 27709

1430
1431 ©2004, GlaxoSmithKline. All rights reserved.

1432
1433 Month 2004

RL-